

Division of Molecular and Vascular Medicine



William C. Aird, MD,
Chief



J. Peter Oettgen, MD,
Associate Chief

● Overview

The Division of Molecular Medicine is located on the 6th and 7th floors of the Dana building on BIDMC's East campus. The goal of the Division is to create the first-of-its-kind bench-to-bedside program in vascular/endothelial biomedicine. The Division consists of 6 investigators with primary appointments and 3 investigators with secondary appointments to the Division (Drs. Ananth Karumanchi, Peter Oettgen and Nathaniel Shapiro).

● Educational Programs

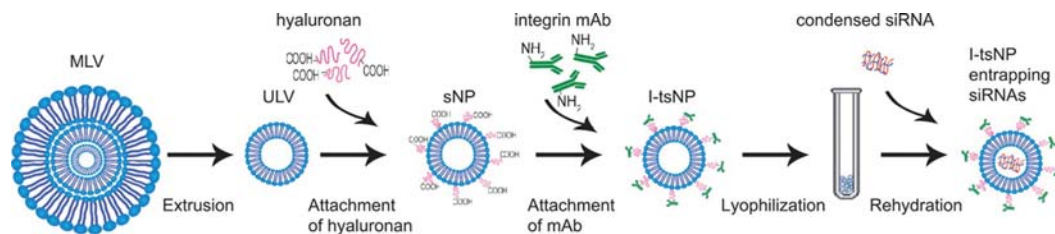
Dr. Aird directs a course in Health Sciences and Technology (HST) called "Blood vessels and endothelial phenotypes in health and disease" (HST-527) and is the founding co-Director of an annual one week course in Comparative Physiology for BIDMC medical residents at Mount Desert Island, Maine. Dr. Alan Rigby directs the Hematology Module of that course, and Dr. Marianne Grant participates as a faculty member. Dr. Christopher Carman lectures in the Harvard Medical School Immunology 202 (Imm202) and Human Physiology and Pathophysiology (DMS220) courses.

● Research Activities

Research Funding • AY'07

Federal Direct	2,060,193
Federal Indirect	1,026,754
Other Direct	1,634,019
Other Indirect	71,909

The Division occupies 12,000 square feet of laboratory space, and consists of some 50 post-doctoral fellows, students, and research assistants. Faculty members cover a wide breadth of basic research. Dr. Ruhul Abid studies the role of redox signaling in vascular biology and has an interest in the role of forkhead transcription factors in the endothelium. Dr. Aird's laboratory studies the spatial and temporal dynamics of the endothelium. Specifically, they study the mechanisms of cell signaling *in vitro* and *in vivo*, transcriptional networks in the endothelium, and the role of the endothelium in pathophysiological states such as sepsis and tumors. The Alper lab studies the molecular cell physiology of ion transporters and channels, with special interests in cell pH and volume regulation, and ionic signaling mechanisms. Dr. Carman employs intravital microscopy and other cutting edge



- Schematic for generation of novel integrin-targeted nanoparticle siRNA delivery system. Multilamellar vesicles are extruded to form a unilamellar vesicles (ULV) with a diameter of ~100 nm. Hyaluronan is covalently attached to the ULV and in turn an integrin-specific monoclonal antibody is attached to the to the hyaluronan. siRNAs are entrapped by rehydrating lyophilized nanoparticles with water containing protamine-condensed siRNAs.

● Faculty

Ruhul Abid, MD, PhD	Peter Oettgen, MD
William Aird, MD	Erzsébet Ravasz
Seth Alper, MD	Regan, PhD
Christopher Carman, PhD	Alan Rigby, PhD
Marianne Grant, PhD	Nathaniel Shapiro, MD
Ananth Karumanchi, MD	

imaging technologies to dissect mechanisms of leukocyte-endothelial cell interactions. Dr. Grant employs multidimensional NMR spectroscopy to study the structural biology of proteins with regulatory and signaling function, with the goal of using protein structure to gain mechanistic insight into protein function. The major focus of Dr. Karumanchi's group is the role of angiogenic factors in the pathogenesis of pre-eclampsia. Dr. Oettgen's laboratory studies the role of selected transcription factors in the regulation of vascular inflammation, angiogenesis, vascular development, and endothelial differentiation. Dr Rigby's laboratory is focused on using structural biology to better understand anticoagulation, apoptosis, gene expression and receptor ligand interactions, with a particular interest in structure-based *in silico* drug discovery.

● Awards and Honors

Dr. Karumanchi received a Howard Hughes Investigator Award.

● Selected Publications

Abid R, Spokes KC, Shih SC, Aird WC. NADPH oxidase activity selectively modulates vascular endothelial growth factor signaling pathways. *J Biol Chem* 2007; 282:35373-85.

Carman CV, Springer TA. Trans-cellular migration: cell-cell contacts get intimate. *Curr Opin Cell Biol*, 2008; 20:533-40.

Clark JS, Vandorpe DH, Chernova MN, Heneghan JF, Stewart AK, Alper SL. Species differences in Cl⁻ affinity and in electrogenicity of SLC26A6-mediated oxalate/

Cl⁻ exchange correlate with the distinct human and mouse susceptibilities to nephrolithiasis. *J Physiol* 2008; 586:1291-306.

Grant MA, Lazo ND, Lomakin A, Condrón NM, Arai H, Yamin G, Rigby AC, Teplow DB. Familial Alzheimer's disease mutations alter the stability of the amyloid beta-protein monomer folding nucleus. *Proc Natl Acad Sci USA* 2007; 104:16522-7.

Ni W, Zhan Y, He H, Maynard E, Balschi JA, Oettgen P. Ets-1 is a critical transcriptional regulator of reactive oxygen species and p47phox gene expression in response to Angiotensin II. *Circ Res* 2007; 101:985-94.

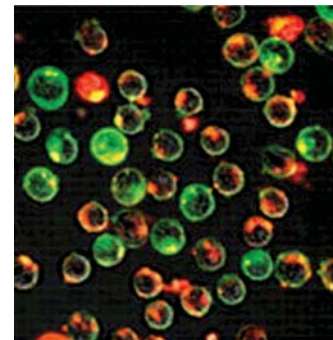
Parikh SM, Karumanchi SA. Putting pressure on pre-eclampsia. *Nat Med* 2008; 14:810-2.

Peer D, Park EJ, Morishita Y, Carman CV, Shimaoka M. Systemic leukocyte-directed siRNA delivery revealing cyclin D1 as an anti-inflammatory target. *Science* 2008; 319:627-30.

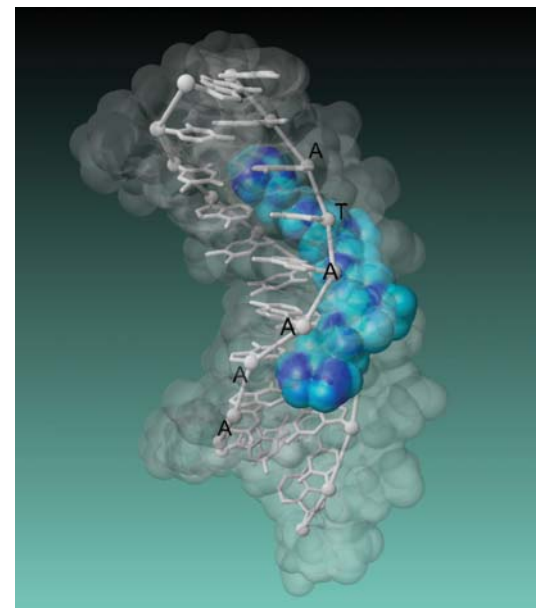
Shapiro NI, Yano K, Okada H, Fischer C, Howell M, Spokes KC, Ngo L, Angus DC, Aird WC. A prospective, observational study of soluble FLT-1 and vascular endothelial growth factor (VEGF) in sepsis. *Shock* 2008; 29:452-7.

Tan K, Duquette M, Liu JH, Shanmugasundaram K, Joachimiak A, Gallagher JT, Rigby AC, Wang JH, Lawler J. Heparin-induced cis- and trans-dimerization modes of the thrombospondin-1 N-terminal domain. *J Biol Chem* 2008; 283:3932-41.

Yano K, Okada Y, Beldi G, Shih SC, Bodyak N, Okada H, Kang PM, Lusinskas W, Robson SC, Carmeliet P, Karumanchi SA, Aird WC. Elevated levels of placental growth factor represent an adaptive host response in sepsis. *J Exp Med* 2008; 205:2623-31.



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● Confocal microscopy demonstrating integrin-specific intracellular delivery of Cy3-siRNA into murine splenocytes. Alexa 488-labeled nanoparticles (green) and Cy3-siRNA cargo (red) are visualized. (Courtesy of Dr C. Carman.)



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● Netropsin's mechanism of action within the minor groove AT-track of the Oct site in the NOS2 promoter disrupts HMG1A1 transactivation of the NOS2 promoter and improves survival outcomes in murine endotoxemia. Grant et al, *Biochem J* 2008, in press. (Courtesy of Dr C. Carman.)